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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/859,722	05/17/2001	William Stuart Somers	16163-004001 / AM100225	2770

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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/859,722	SOMERS ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 36-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16 and 36-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Status of the Application

2. The response to the previous Office action and amendments to the claims and specification filed 06 November 2006 are acknowledged. Claims 15, 16 and 36-60 are pending and subject to examination.

Withdrawal of Rejections/Objections

3. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 –2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention. The details of the rejection can be found in the previous Office action in Section 13.

Response to Arguments

Withdrawn Rejections:

6. Applicant's arguments with respect to the rejection of claims 15, 16 and 36-60 under 35 U.S.C. 101 for lack of utility have been fully considered and are persuasive. The rejection of said claims has been withdrawn.

7. Applicant's arguments with respect to the rejection of claims 15, 16 and 36-60 under 35 U.S.C. 112 2nd paragraph as recited in Sections 12, 14 and 15 in the previous Office action have been fully considered and are persuasive. The rejections of said claims have been withdrawn.

8. The rejection of claims 15, 16 and 36-30 under 35 U.S.C. 103(a) as recited in the previous Office action in Sections 16-19 are withdrawn. The rejections are withdrawn in view of the amendments to the claims which require the use of a P-selectin LE crystal which is not taught in any of the previous prior art. However, new rejections of the same claims are made under a different statute, wherein the new rejections are necessitated by amendment.

Maintained Rejections:

9. Applicant's arguments with respect to the rejection of claims 15, 16 and 36-60 under 35 U.S.C. 112 2nd paragraph as recited in Section 13 of the previous Office action and reiterated above have been fully considered but they are not persuasive.

Applicants assert that the metes and bounds of the term "relative structural coordinates" is clear because it is well known to those skilled in the art of protein crystallography. However, the examiner disagrees with this assertion. The term

'relative' is a subjective term which is not defined. While those skilled in the art might be able to comprehend roughly what one might mean by using the term, ten different crystallographers will likely give ten different answers to what the metes and bounds of this limitation are. Furthermore, because the world of protein crystallography deals in such a minute degree of measurements in angstroms (10×10^{-10} meters), an angstrom here or an angstrom there is an enormous variation and it is not clear from said limitation what the variance is or might be. Thus, the further limitation that the coordinates are not more than an rmsd of ± 1.5 Å from the relative structural coordinates of Figures 2, 3 or 5 is also ambiguous because how is one supposed to know even where to measure said 1.5 Å from if the starting point is not defined and is merely relative? Finally, Applicants own definition of "relative" structural coordinates on p. 15, lines 7-19 of the specification states that the coordinates can come from NMR models, homology models, molecular replacement models all of which may be subject to various mathematical manipulations. Thus, the recitation of 'relative structural coordinates' appear to be non-limiting.

New Rejections/Objections

Claim Rejections - 35 USC § 112 – 2nd paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

11. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. The claims are drawn to *in silico* methods for identifying agents that interact with P-selectin LE by providing a crystal comprising a P-selectin LE and generating a 3-D model using the relative structural coordinates. However, there is a gap in the method steps because merely generically providing a crystal says nothing about subjecting said crystal to X-ray diffraction and solving the structure in order to obtain the structural coordinates. At the moment, the claims require nothing to be done to the crystal once it is provided so it is either a non-limitation in the claim which is surplus to requirement or said crystal needs to be positively acted upon and used in the method steps.

Claim Rejections - 35 USC § 112 – 1st paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement:

13. Claim 15, 16 and 36-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent that interacts with P-selectin LE by providing a crystal consisting of P-selectin LE selected from the group consisting of: a) a P-selectin LE crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of

SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å; determining the structure of said crystals, generating a 3-D model of P-selectin LE having the structural coordinates of Figures 2, 3 or 5 and employing said 3-D structure to design or select an agent that interacts, does not reasonably provide enablement for the method which uses any P-selectin LE crystal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE. Thus, the claim is unlimited in the number and variance of different P-selectin LE crystals that can be used in the claims because the protein within the crystal is not limited to any particular P-selectin protein. Thus the protein can be derived from a variety of species, wherein said proteins are also not limited to any particular specific protein sequence and thus would encompass any and every fragment, derivative or homolog of any of these P-selectin LE proteins. Furthermore, "a crystal comprising a P-selectin LE" has been interpreted as encompassing any ligand bound to P-selectin LE of the crystal. However, the specification only adequately describes how to make three protein crystals that fall within the scope of the claims and

which are described in the specification on pp. 31-32. For instance, P-selectin LE apo-form, was crystallized at 18°C from a solution containing 10 mg/ml prteoin, 100 mM Tris-HCL (pH 8.5), 150 mM NaCl, 12 mM $CaCl_2$, 10% (v/v) MPD and 10% (w/v) Peg 6k. The transfer solutions necessary for flash-cooling are also described. This kind of detail is necessary and enables one of ordinary skill in the art to reproduce said crystals. However, the countless other crystals which fall within the scope of the claims are not described nor even contemplated in the specification. Because of the extreme unpredictability of crystallizing any protein, even those that have been described previously, the scope of the claims exceed that which is enabled and a skilled artisan would expected to have to determine, or try to determine *de novo* crystallization conditions in order to make and/or use the claimed invention. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in

determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In order to make the protein crystals encompassed by the scope of the claims, the following must be clear: (a) the preparation and chemical composition of the molecules to be crystallized (recited unambiguously) and (b) the crystallization conditions, including methods and reagents used. Applicants have met this burden for three P-selectin LE crystal species in the specification (described on pp. 31-32); however, as stated *supra*, the claims encompass a large number crystals which have not been described and are by no means trivial to produce. Undue experimentation would be expected in the instant case because even the smallest change in any parameter in crystallizing a protein can have enormous consequences. McPherson (Eur. J. Biochem. 1990, 189:1-23) outlines 25 different parameters which do or could affect crystallization (see Table 2, p. 13). It is stated (p. 13, 2nd column; *Factors influencing protein crystal growth*):

> Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins.

Thus, it is not enough to have the crystallization conditions of a "native" protein. Rather, what would be required is precise instructions about how to make each and every protein crystal in order to avoid undue experimentation (e.g. conditions for each and P-selectin LE crystal produced with P-selectin protein from any species and which may be derivatives, homologues or fragments thereof). However, there is no direction or guidance in the specification above or beyond the description of the P-selectin LE crystals from humans and the details of a different protein all together E-selectin. The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, Methods in Enzymology, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2; and Cudney, Rigaku Journal, 1999,

Vol. 16, No. 1, pp. 1-7). Furthermore, the prior art regarding crystallization of P-selectins is of limited assistance because there are no P-selectin proteins from human or other species that are crystallized in the apo form or in complex form.

However, since the claims currently are broader than what they are enabled for, when all things are considered and the Wands factors are treated on their merits, the claims are not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the claimed invention.

Written Description:

14. Claims 15, 16 and 36-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE. Thus, the claims are intrinsically drawn to large number of species of P-selectin crystals containing P-selectin proteins from any species and which are derivatives, homologues or fragments thereof and thus the claims possess a large genus of crystals. Also, as noted above, the crystal can have any ligand bound to the P-selectin LE. However, the specification only adequately describes three species in terms of both structure and function which belongs to this genus.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes three species of a P-selectin LE crystals that fall within the instant genera of crystals, those being: a) a P-selectin LE crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal consisting of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8

complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å. These particular crystals are the only species representative of the genus based upon the description of the proteins that make up the crystal (e.g. SEQ ID No:), and the characteristics of the crystal itself, e.g. space group and unit cell parameters.

While the claim language recites a function for the instant genera of crystals (that of P-selectin lectin and EGF binding domains (LE)), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant crystal genus as a whole. In general, for a species of crystal to be adequately structurally described, the following must be effectively disclosed in the specification and *in the claims*: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. Alternatively, where the crystal is described by product-by-process, the crystal must be adequately described by reciting the exact and full conditions for crystallization (e.g. method, exact buffer, salt and/or additive concentrations, pH, temperature) and the method claims must include the same in the same claim.

It is very well known in the art that a singular chemical composition can crystallize differently based on the crystallization conditions and the protein to be crystallized (e.g. variants, mutants, homologs, derivatives, etc. – also see scope of enablement rejection above), and the space group and unit cell dimensions of a crystal

of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). However, based on the instant specification, the chemical composition, space group, and unit cell dimensions and methods of making thereof encompassed by the breadth of the claims, is unpredictable to one of skill in the art. While, the three P-selectin LE crystal species noted above have adequately met the burden of being adequately described in the specification and indeed are three species found within the genus, this is not sufficient. For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim by describing a sufficient number of representative species. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) *("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...")* *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

However, because the composition of the crystals encompassed by the breadth of the claims (e.g. an unlimited number or P-selectin LE variants) and also the space groups and unit cell parameters of these variant crystals which are encompassed by the genus, can not be envisioned by these three crystal species because of the extensive unpredictability in the art of crystallography (see Cudney et al., pp. 1-7, Drenth et al., Chapter 1, p. 19, 4th paragraph, lines 1-2; and McPherson et al., p. 13), then said

species can not be considered to be representative of the entire genus. Therefore, claims drawn to the instant genera of P-selectin LE crystals are not adequately described.

Conclusion

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
17 January 2007

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER